IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC,	)	
Plaintiffs,	)	C.A. No. 06-286-GMS
v.	)	
BARR LABORATORIES, INC.,	)	**REDACTED PUBLIC VERSION**
Defendant.	)	

PLAINTIFFS' OPPOSITION TO BARR LABORATORIES, INC.'S MOTION *IN LIMINE* TO EXCLUDE ANY DOCUMENTS RELATED TO BARR'S ANDA TO SHOW PROOF OF COPYING

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Dated: April 7, 2008

PRELIMINARY STATEMENT

Barr has asked this Court to "exclude evidence regarding Barr's ANDA and the development of Barr's ANDA product to establish 'copying' as part of Plaintiffs' case on secondary considerations of nonobviousness." (Barr Motion *In Limine* ("Barr Mot.") at 1.) As an initial matter, it is not clear what documents Barr seeks to exclude. Barr's ANDA and product development documents are indisputably relevant to infringement, and therefore Barr's motion should be denied to the extent it seeks to exclude those documents.[1]

Regardless of the ambiguity, Barr's motion should be denied because there is no legal basis to exclude evidence of copying in this case. Barr cites two cases that purportedly support its argument that "[e]vidence of copying in ANDA cases . . . is largely irrelevant to nonobviousness." (Barr Mot. at 2.) However, Barr's cases are inapposite because they concern patents on active pharmaceutical ingredients, not formulations (like the patents-in-suit here). Moreover, most cases have reached the opposite conclusion: evidence of copying in ANDA cases is relevant, objective evidence of nonobviousness in any context.

ARGUMENT

According to the Federal Circuit, "evidence bearing on [the] issue of nonobviousness is never of 'no moment,' [it] is always to be considered and accorded whatever weight it may have." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) (citation omitted). "Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not." *Id. See also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, No. 2007-1223, 2008 U.S. App. LEXIS 6786, at *16 (Fed. Cir. Mar. 31, 2008) ("this

[1] Barr has included a portion of its ANDA in its own list of trial exhibits. Thus, Barr cannot be seeking to exclude its ANDA completely.

evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness"). Copying of the claimed invention is well established as objective evidence of nonobviousness. *See, e.g., Advanced Display Systems, Inc. v. Kent State University*, 212 F.3d 1272, 1285 (Fed. Cir. 2000) ("an accused infringer's close copying of the claimed invention, rather than one in the public domain, is indicative of nonobviousness").

In this case, there is clear evidence that Barr copied the formulation of Nasacort® AQ, Aventis's commercial embodiment of the patented invention. The company that makes Barr's ANDA product, Agis Industries (1983) Ltd. (now known as Perrigo Israel Pharmaceuticals Ltd.), began its product development process by submitting a FOIA request to the FDA to obtain a list of the active and inactive ingredients in Nasacort® AQ. (Ex. 1, Rebuttal Expert Report of Robert Y. Lochhead at ¶ 165.) With that information in hand, Agis began "reverse engineering" Nasacort® AQ, with the goal of replicating the Nasacort® AQ formulation identically. (*Id.* at ¶ 166.) Agis's laboratory notebooks, as well as additional documents and testimony, show that Agis managed to reverse engineer the Nasacort® AQ formulation after about five months of experimentation, from August 1998 to January 1999. (*Id.* at ¶¶ 166-69.) The formulation of Barr's ANDA product contains the same inactive ingredients, in essentially identical quantities, as those in Nasacort® AQ. (*Id.* at Table II.)

Barr argues that it copied the claimed invention "not because of the patented invention but because of regulatory requirements." (Barr Mot. at 2.) However, that is simply untrue: FDA regulations require ANDA applications to use the same active pharmaceutical ingredient as that in the reference listed drug, but do not mandate copying the entire formulation. No statute or regulation required Barr to use the same *inactive ingredients* as those in the Nasacort® AQ

formulation (and claimed in the patents-in-suit). (Ex. 2, Expert Report of Donald O. Beers at ¶ 12.) In fact, the applicable regulation expressly states the exact opposite:

> Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application *may include different inactive ingredients* provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

21 C.F.R. § 314.94(a)(9)(v) (2007) (emphasis added); (Ex. 2 at ¶ 12.) Thus, there was no "regulatory requirement" that Barr copy the Nasacort® AQ formulation.

Barr further argues that "Perrigo developed the ANDA product with the same formulation as Nasacort® AQ, the branded product, solely in order to meet the FDA guidance." (Barr Mot. at 3). Again, that is untrue. The guidance Barr refers to was not promulgated until June 1999 – ten months *after* Agis began reverse engineering the Nasacort® AQ formulation. When asked for an explanation of what, if anything, Agis relied on when it began its development work, Perrigo's corporate witness on product development could not offer one:

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* * *

REDACTED

REDACTED

(Ex. 3, Zeevi Tr. at 67:7-68:8) (objections omitted). In any event, the later-promulgated draft FDA guidance sets forth only nonbinding *recommendations*, not requirements.[2] (Ex. 2 at ¶¶ 4-11.) Accordingly, the evidence suggests that, rather than being motivated to copy Nasacort® AQ by some "regulatory requirement" or FDA guidance, Barr copied the formulation of Nasacort® AQ because that was the "path of least resistance" to developing a product. (Ex. 2 at ¶ 9.)

Based on two cases concerning patents on active pharmaceutical ingredients, Barr argues that evidence of copying in ANDA cases "is largely irrelevant to nonobviousness because the ANDA process effectively requires an ANDA applicant to copy the brand drug referenced in its ANDA." (Barr Mot. at 2 (citing *Aventis Pharma Deutschland GMBH v. Lupin Ltd.*, No. 2:05cv421, 2006 U.S. Dist. LEXIS 48246 (E.D. Va. July 17, 2006); *Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, No. IP 02-0512-C-B/S (S.D. Ind. July 29, 2004).) Those cases address an entirely different situation because ANDA applicants must use the same active ingredient in their generic drug products. It is undisputed, however, that ANDA applicants are permitted to use different *inactive ingredients*. Thus, in this case Barr could have developed a formulation using the same active ingredient as that in Nasacort® AQ, but different inactive ingredients (in which case Plaintiffs would not accuse Barr of copying). Instead, Barr chose to copy the entire patented formulation of Nasacort® AQ, an action not compelled by any authority.

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[2] The FDA guidance remains only *draft* guidance, making it especially unreliable. Ordinarily, FDA first develops guidance documents in draft form and then issues a final guidance. Expressly rejecting requests to "make mandatory the recommendations" in the draft guidance, FDA has not finalized any guidance relevant to this case. (Ex. 2 at ¶¶ 4-11).

Furthermore, even in ANDA cases where the patents-in-suit are directed to the active ingredient of a drug product, numerous courts have relied on copying of the active ingredient as objective evidence of nonobviousness. *See, e.g.*, *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 438 F. Supp. 2d 479, 496 (D. Del. 2006) (Farnan, J.) ("[t]he success of Lexapro® and its benefits compared with other SSRIs is also supported by the efforts of generic drug manufacturers, including Defendants, to copy the claimed invention"); *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 1088 (D. Del. 2005) (Farnan, J.) ("the fact that Ranbaxy has chosen to copy Lipitor® in its ANDA further demonstrates the success and efficacy of Lipitor® compared with other available products"), *rev'd on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006); *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 348 F. Supp. 2d 713, 759 (N.D. W.Va. 2004) ("the Court finds that Mylan's decision to copy LEVAQUIN instead of FLOXIN is significant evidence of non-obviousness, particularly in light of Mylan's lack of success in marketing its own respiratory quinolone"). *See also In re Certain Crystalline Cefadroxil Monohydrate*, 15 U.S.P.Q.2d 1263, 1271 (ITC 1990) (rejecting the argument that "copying should be accorded no weight in the obviousness determination because it is done solely to facilitate FDA approval"). In view of cases such as these, at least two Third Circuit courts recently denied motions *in limine* to exclude evidence of copying in ANDA cases. *See Pfizer Inc. v. Mylan Labs., Inc.*, No. 02cv1628, 2006 U.S. Dist. LEXIS 83857 (W.D. Pa. Nov. 17, 2006); *Pfizer Inc. v. Teva Pharms. USA, Inc.*, No. 04-754 (JCL), 2006 U.S. Dist. LEXIS 77967 (D.N.J. Oct. 26, 2006).

CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that the Court deny Barr's Motion *In Limine* to Exclude Any Documents Related to Barr's ANDA to Show Proof of Copying.

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Dated: April 7, 2008

EXHIBIT 1

REDACTED

EXHIBIT 2

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

AVENTIS PHARMACEUTICALS INC. and SANOFI-AVENTIS US LLC, Plaintiffs, v. BARR LABORATORIES, INC., Defendant.	Civil Action No.: 06-286 (GMS)

EXPERT REPORT OF DONALD O. BEERS

I, Donald O. Beers, hereby declare as follows:

A. Background

1. I am a Partner in the law firm of Arnold & Porter LLP, in Washington, D.C., specializing in food and drug law. I received a B.A. in 1971 from Dartmouth College and a J.D. in 1974 from Columbia Law School. I then clerked for the Honorable Milton Pollack of the United States District Court, Southern District of New York. Since then, I have been practicing food and drug law. In my practice, I counsel FDA-regulated companies and represent them before the FDA, in Congress and in the courts on a wide variety of FDA-regulatory and related issues. I served the Food and Drug Administration for over ten years as Associate Chief Counsel for Drugs, Associate Chief Counsel for Enforcement, and attorney in the Office of Chief Counsel. I also taught food, drug and medical device law as an adjunct professor at the University of Pennsylvania Law School in 1982-1984. I speak often, in this country and internationally, on issues relating to the drug approval process. I am the author of a well-known treatise, Generic and Innovator Drugs: A Guide to FDA Approval Requirements, the sixth edition of which was published in 2004. A copy of my *curriculum vitae* is attached as Exhibit A.

2. I have been retained by the law firm of McDonnell Boehnen Hulbert & Berghoff LLP in relation to the above-captioned lawsuit to provide my opinions on a number of topics. I am being compensated for my work on this case at my regular rate of $705 per hour. I have been asked to provide: (1) my opinion of whether FDA regulations and guidance required Barr Laboratories, Inc. ("Barr") to copy the formulation for Nasacort AQ® in order to obtain FDA approval to market a generic triamcinolone acetonide ("TAA") nasal spray product; and (2) my interpretation of FDA regulations concerning clinical studies of a new drug, including the confidentiality of such clinical studies. In the past five years, I have served as an expert witness in three matters: an arbitration between Pharma, LLC and Dr. Reddy's Laboratories et al., American Arbitration Association; a valuation dispute between Adams Respiratory Therapeutics and J-Med Pharmaceuticals, Inc.; and *Elan Pharmaceuticals, Inc. v. N.V. Organon*, Civil Action No. 04 CV 2002 (JGK), S.D.N.Y.

3. In forming my opinions, in addition to applying my own knowledge, I have considered the following materials:

a. The Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 201 et seq. (the "FFDCA").

b. Federal Regulations referred to herein.

c. "Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), June 1999, ("1999 FDA Draft Guidance Document"). A copy of the 1999 Draft Guidance Document is attached as Exhibit B.

d. "Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action," U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), April 2003, ("2003 FDA Draft Guidance Document"). A copy of the 2003 Draft Guidance Document is attached as Exhibit C.

e. February 22, 2006 letter from Randall W. Lutter, Ph.D., Acting Associate Commissioner for Policy and Planning, Food and Drug Administration, to Frederick H. Branding, C. Elaine Jones, Ph.D., William M. Zoffer and Charles J. Raubicheck, responding to multiple citizen petitions submitted to docket nos. 2004P-0206/CP1; 2004P-0239/CP1, SUP 1, SUP 2 & PSA 1; 2004P-0348/CP1 & SUP 1; and 2004P-0523/CP1 & PSA1; ("2006 FDA Petition Response"). A copy of the 2006 FDA Petition Response is attached as exhibit D.

B. Copying

4. Publishing guidance documents is a method by which FDA provides its view on subjects when it is not addressing those subjects with binding rules. FDA's regulations concerning "good guidance practices" are very clear that there is no obligation to follow a guidance document. *See* 21 C.F.R. 10.115(d)(1)-(2):

> *Are you or FDA required to follow a guidance document?*
>
> (1) No. Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA.
>
> (2) You may choose to use an approach other than the one set forth in a guidance document. However, your alternative approach must comply with the relevant statutes and regulations. FDA is willing to discuss an alternative approach with you to ensure that it complies with the relevant statutes and regulations.

5. FDA often, as in this case, first develops guidance documents in draft form. FDA then provides an opportunity for the public to submit comments on the draft. FDA may then alter the draft text before it issues a final guidance document. Because of the potential that it may be changed, there is less reason to follow the suggestions in a draft guidance document than there is to follow those set out in a final guidance document.

6. The 1999 FDA Draft Guidance Document and the 2003 FDA Draft Guidance Document provide recommendations for bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action, such as Barr's generic version of Aventis's Nasacort AQ® product. The 2003 document is an updated version of the 1999 document. FDA has not provided a further update since publishing the 2003 document.

7. Both guidance documents are draft documents. Both are marked "Draft – Not for Implementation." Each also states: "This guidance document is being distributed for comment purposes only." FDA has not issued final guidance for bioavailability and bioequivalence studies for nasal aerosols and nasal sprays.

8. Both the 1999 FDA Draft Guidance Document and the 2003 FDA Draft Guidance Document recommend that the inactive ingredients in a suspension formulation of a generic nasal spray, such as Barr's generic TAA nasal spray product, be qualitatively (Q_1) the same and quantitatively (Q_2) essentially the same as the inactive ingredients in the formulation of the reference listed drug. In this case, the reference listed drug is Nasacort AQ®. *See* 1999 Draft Guidance Document, p. 7; 2003 Draft Guidance Document, p. 8. In addition, the 2003 document states: "Quantitatively *essentially the same* has been determined by CDER to mean that the concentration or amount of the inactive ingredient(s) in the test product would not differ by more

than 5 percent of the concentration or amount in the reference listed drug." 2003 Draft Guidance Document, p. 8.

9. Based on the 1999 and 2003 Draft Guidance Documents, copying Aventis's Nasacort AQ® formulation would have been the "path of least resistance" for Barr, at least in terms of FDA review. In other words, if Barr had submitted an Abbreviated New Drug Application ("ANDA") with Nasacort AQ® as the reference listed drug, but Barr's formulation was not qualitatively the same and quantitatively essentially the same as Nasacort AQ®, then the FDA probably would have scrutinized Barr's ANDA more carefully. Although not certain, FDA might have taken longer to approve Barr's ANDA.

10. Neither the 1999 FDA Draft Guidance Document nor the 2003 FDA Draft Guidance Document required Barr to copy Aventis's Nasacort AQ® formulation. In fact, both documents state that they contain nonbinding recommendations, not requirements. The 1999 document states: "This guidance represents the Agency's current thinking on product quality information related to inhalation aerosols and metered dose spray pumps for nasal delivery. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both." 1999 FDA Draft Guidance Document, p. 1, n. 1. Similarly, the 2003 FDA Draft Guidance Document states: "This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations." 2003 FDA Draft Guidance Document, p. 2.

11. In 2006, FDA responded to multiple citizen petitions concerning fluticasone propionate nasal spray suspension products. *See* 2006 FDA Petition Response. In that response, FDA directly addressed two petitions that asked FDA to convert its nonbinding recommendations in the 2003 FDA Draft Guidance Document into mandatory requirements. FDA rejected this request, stating: "FDA disagrees with Bell's and Frommer's petitions to the extent that they request FDA make mandatory the recommendations in the 2003 draft BA/BE guidance." 2006 FDA Petition Response, p. 3, n. 4. In the same response, FDA stated: "Guidance documents do not restrict FDA's ability to consider methodologies other than those articulated, nor do they restrict or replace the Agency's obligation to make a determination as to whether individual applications meet statutory requirements." *Id.*, p. 6 (referencing 21 C.F.R. 10.115(d)). Thus, the 2006 FDA Petition Response makes it clear that the 1999 and 2003 Draft Guidance Documents contain only nonbinding recommendations.

12. No statute or regulation required Barr to copy Aventis's Nasacort AQ® formulation. In fact, the applicable regulation expressly states the opposite. 21 C.F.R. 314.94(a)(9)(v), which is entitled "Inactive ingredient changes permitted in drug products," states as follows: "Generally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug identified by the applicant under paragraph (a)(3) of this section. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." The 2003 FDA Draft Guidance Document specifically refers to this regulation. *See* p. 8, n. 8. Thus, the

applicable regulation expressly permits makers of generic nasal sprays to pursue FDA approval of formulations that are not qualitatively the same as the formulation of the reference listed drug.

13. In view of the foregoing, it is my opinion that Barr was not required by any statute, regulation or FDA guidance document to copy Aventis's formulation for Nasacort AQ® in order to obtain FDA approval for a generic TAA nasal spray product. In fact, the applicable statutes, regulations and FDA guidance permitted Barr to use different inactive ingredients in its generic TAA nasal spray product than those found in Nasacort AQ®.

C. Clinical Studies

14. A new drug may not be marketed in the United States unless the FDA has first approved a New Drug Application ("NDA") or and ANDA that covers that drug. 21 U.S.C. 355(a). Thus, Aventis would not have been permitted to market Nasacort AQ® until the NDA that it submitted for that drug was approved by FDA.

15. The FFDCA requires "adequate and well-controlled investigations" as a basis for approval of an NDA. 21 U.S.C. 355(d). Such investigations often include phase 3 studies, such as those conducted by Aventis in support of its NDA for Nasacort AQ®.

16. In 21 C.F.R. 312.21(c), FDA defines a "phase 3" study as follows:

> Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

Phase 3 studies follow Phase 1 (preliminary studies, often in a few normal subjects) and Phase 2 studies (the first controlled clinical trials, usually in a relatively small number of subjects).

17. Pursuant to FDA regulations, the contents of an NDA are kept confidential until the time of approval or abandonment of the NDA. 21 C.F.R. 314.430(b), (c). Thus, in this case, those regulations required FDA to keep the results of Aventis's phase 3 studies of Nasacort AQ® confidential prior to the approval of the NDA.

18. Even after an NDA is approved, it is often the case that protocols and other parts of an NDA will not be released to the public, though summaries of the results of the studies may be released. This is because FDA regulations provide that the full effectiveness submission will not be released if "the applicant shows that extraordinary circumstances exist." 21 C.F.R. 314.430(e). This reflects the underlying law, 21 U.S.C. 505(l). As a general rule, FDA has accepted the position of innovators that extraordinary circumstances prevent the release of safety and effectiveness data. Even if the extraordinary circumstances exception is not effectively invoked, a protocol will still not be released if it is shown to be protected as a trade secret or confidential information. 21 C.F.R. 314.430(e)(3).

I declare under penalty of perjury that the foregoing is true and correct. Executed in Washington, D.C., January 31, 2008.

Donald O. Beers

EXHIBIT 3

REDACTED